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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/345,148	06/30/1999	ANDREW H. SEGAL	3378/80490	9870

29933 7590 06/29/2005

PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/345,148	SEGAL, ANDREW H.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/8/05

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 1, 3-17, 19-68, 70

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 15, 16, 19, 20, 27, 30-68

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1, 3-14, 17, 21-26, 28, 29, 70

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 4/8/05, has been entered.
Claim 7 has been amended.

Claims 2, 18 and 69 have been canceled previously.

Claims 1, 3-17, 19-68 and 70 are pending.

For the record, applicant's election of the species CD40-specific antibody, alpha chain of C3b and IL-2 in Paper No. 10, filed 4/5/01 and in Paper No. 13, filed 12/19/01, has been acknowledged.

Claims 1, 3-14, 17, 21-26, 28, 29 and 70 are being acted upon as the elected invention

Claims 15-16, 19, 20, 27 and 30-68 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected inventions and/or species.

2. Upon reconsideration of applicant's arguments with respect to the recitation of "admixture with a ligand for CD40 which comprises a heterologous cell membrane binding moiety", New Grounds of Rejection have been set forth herein.

4. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

5. Claims 1, 3-14, 17, 21-26, 28, 29 and 70 are rejected under 35 U.S.C.§ 103(a) as being unpatentable over Grossmann et al. (Human Gene Therapy 8 : 1935-1943, 1997) AND/OR Kato et al. (J. Clin. Invest. 101 : 1133-1141, 1998) in view of NEWLY ADDED Hoo (U.S. Patent No. 5,891,432), Maraskovsky et al. (U.S. Patent No. 6,017,527), (Dullforce et al. (Nature Medicine 4: 88-91, 1998; 1449), Heath et al. (WO 94/04570), Heath et al. (Eur. J. Immunol., 24: 1828-1834, 1994), well known use of engineering attachment of a lipid such as a long-chain fatty acid to a molecule such as a peptide to permit the complex to stably associated with the plasma membrane , including the use of palmitate as acknowledged on pages 64- 67 of the instant specification (see Engineered Opsonins, Cytokines or Ligands for CD40 Containing a Lipid), including the teachings of McHugh et al. (PNAS 92: 8059-8063, 1995) and Jacquier-Sarlin et al. (Immunology 84: 164-170, 1995).

Hoo has been added as additional reference to address applicant's arguments with respect to the recitation of "admixture with a ligand for CD40 which comprises a heterologous cell membrane binding moiety".

Hoo teaches cellular vaccines comprising membrane-bound fusion proteins, including immumodulatory molecules, including immunostimulatory (as well as immunosuppressive) operatively fused to a heterologous membrane attachment domain (see entire document, including Background of the Invention, Summary of the Invention and Detailed Description of the Invention). It is noted that Hoo also teaches that the vaccine can contain CD40L ligand (see columns 18-19, overlapping paragraph).

Further, given the teachings of the references of record reiterated for applicant's convenience below, including the teachings of vaccinating for tumor antigens, including the use of CD40:CD40 ligand pathway and IL-2 and the teachings of McHugh et al. for teaching the provision of co-stimulatory signals in conjunction with tumor cell vaccination, the ordinary artisan would have been motivated at the time the invention was made to combine the co-stimulatory signal of anti-CD40 antibodies, taught by Dullforce et al., Caux and Heath, in conjunction with the tumor cells themselves to vaccinate against tumor cells and/or antigens of interest.

More pointedly to applicant's arguments of record, Hoo provides for the use of immunostimulatory molecules, including reliance upon molecules stimulating via the CD40:CD ligand pathway, fused to a heterologous membrane attachment domain in cellular vaccines, which is consistent with the claimed invention.

Although applicant appears to be arguing that McHugh et al. (PNAS 1995) is limited to B7, McHugh et al. teach the possibility and use recombinant techniques for transmembrane proteins in general and not limited to B7-1, to be converted to GPI-anchored proteins and incorporated into cell membranes after a short incubation periods, thus potentially eliminating the introduction of foreign DNA for tumor immunotherapy (see Introduction, including page 8059, column 2, paragraph 2).

Grossman et al., Kato et al., Maraskovsky et al., Heath et al. and Dullforce et al. as well as newly added Hoo provide for the obviousness of stimulating immune response via the CD40:CD40 ligand pathway at the time the invention was made.

The following is reiterated for applicant's convenience.

Grossmann et al. teach the transgenic expression of CD40L, which acts as a costimulator, to increase immune responses, including immune responses to a weakly immunogenic tumor (see entire document, including the Abstract). Grossman et al. teach that only a few cells need to be engineered to express CD40L to produce the appropriate immune response to the antigen or cell expressing the antigen (see Discussion, including page 1941, column 2, paragraph 3).

Kato et al. teach that CD40-CD40 ligand interaction plays a critical role in immune activation and that expressing a functional ligand for CD40 on a leukemia cell induces the desired immune responses to that leukemia cell but also for unmodified targeted tumor cells (see entire document, including the Abstract). Here, leukemic B cells were infected with a replication defective adenorvirus vector encoding CD40 ligand (see entire document, including Abstract, Results and Discussion).

Grossman et al. and Kato et al. differ from the claimed invention by not admixing a ligand for CD40 which comprises a heterologous cell membrane binding moiety and wherein the ligand is anti-CD40 antibody rather than CD40L.

Maraskovsky et al. teach the methods of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand and IL-2 (see entire document, including column 6, paragraph 1; column 11, paragraph 4). Here, transfecting the dendritic cells to express the cytokines is also taught.

Maraskovsky et al. teach antigens from a number of pathogenic organisms encompassed by the claimed invention, including bacteria, virus tumor associated antigens (see Preparation of Antigens on columns 10-11).

It is noted that Maraskovsky et al. teach that anti-CD40 antibodies have been shown to mediate various biological activities (see column 7, lines 61-65). However, Maraskovsky et al. differs from the claimed methods by not disclosing the administration of agonistic CD40-specific antibodies per se.

Dullforce et al. teach the administration of agonistic CD40-specific antibodies as adjuvants to stimulate B cells and antigen presenting cells against bacterial pathogens (see entire document, including Abstract). While Dullforce et al. focus on T cell-independent immune responses, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the administration of known agonistic anti-CD40 antibodies would have been applicable to various pathogenic organisms and antigens. It is noted that anti-CD40 antibodies stimulate antigen presenting cells and that human B cells are antigen presenting cells.

Heath et al. (Eur. J. Immunol., 1994) teach anti-CD40 antibodies, including various epitopic specificities, that are capable of stimulating immune responses such as B cells as well as the use of such antibodies in infectious diseases and malignancy (page 1833, column 2) (see entire document, including Abstract and Discussion).

Heath et al. (WO 94/0570) teach treating CD40- malignancies by making such CD40- malignancies express CD40 by transformation or liposome fusion, which leads to stimulating T cells and promoting the desired immune response (see entire document, including pages 24-25, overlapping paragraph). Although Heath et al. is describing making a cell CD40+, Heath et al. is clear that liposomes can serve to target to particular tissues or cells displaying the CD40 molecule or its ligand (e.g. see page 23, paragraph 4).

Therefore, the prior art provides for expressing CD40L or anti-CD40 antibodies with or on cells to stimulate desired immune responses to antigens of interest. While these references provide for various means to engineer the cells to express said immunostimulatory CD40L or anti-CD40, these references do not provide explicit teachings of the well known use of engineering a desired molecule for cell expression by engineering said desired molecule with a heterologous cell membrane binding moiety.

Pages 64- 67 of the instant specification (see Engineered Opsonins, Cytokines or Ligands for CD40 Containing a Lipid) provide for a number of teachings that acknowledge the well known use of engineering attachment of a lipid such as a long-chain fatty acid to a molecule such as a peptide to permit the complex to stably associated with the plasma membrane , including the use of palmitate.

Given that co-stimulatory nature of the CD40:CD40 ligand pathway and the co-stimulatory signal provided by anti-CD40 antibodies, the teachings of McHugh et al. are particularly relevant to the instant invention.

In exemplifying potent immune responses to tumor cells, McHugh et al. teach the use introducing costimulatory molecules into membranes via glycosyl-phosphatidylinositol (GPI) as an alternative approach to provide costimulatory molecules to stimulate immune responses of interests (see entire document, including page 8059, column 2, paragraphs 2-3, Materials and Methods, Results and Discussion). McHugh et al. teach that this eliminates the introduction of foreign DNA for tumor immunotherapy, for example, (see Introduction and Discussion). McHugh et al. teach combinations of costimulatory signals to create the optimal target to facilitate many T cell regulatory and effector functions (see page 8063, column 1, paragraph 3).

McHugh et al. focus on tumor immunity, but one of ordinary skill in the art would have been motivated to employ GPI anchored co-stimulatory molecules with immunogenic cells to stimulate immune responses of interest.

Given the teachings and advantages of combining co-stimulatory molecules via alternative methods as taught by the above-mentioned references, one of ordinary skill in the art at the time the invention was made would have been motivated to modify cells of interest (e.g. cells comprising a selected antigen of interest) with GPI anchored agonistic antibodies to increase stimulation to pathogenic organisms.

Therefore, one of ordinary skill in the art would have been motivated to select agonistic CD40 antibodies to stimulate immune responses via CD40:CD40 ligand interactions by expressing anti-CD40 antibody on said cells by a variety of engineering protocols, including the known use of heterologous cell membrane binding moieties via GPI, as taught by McHugh et al., in order to stimulate and increase desired immune response to antigens of interest, including cells expressing tumor antigens or antigens from a variety of pathogenic organisms, including tumor antigens as well as the those antigens encompassed by the bacteria, fungi and parasites.

In addition to the teachings of agonistic CD40-specific antibodies, taught by Maraskovsky et all., Dullforce et al., Heath et al. (Eur. J. Immunol.), and Heath et al. (WO), it was well known and practiced at the time the invention was made to generate recombinant antibodies such as chimeric antibodies, humanized antibodies and fragments thereof to decrease immunogenicity and increase half-life of such recombinant antibodies. Such anti-CD40 antibodies would comprise the idiotypic portion of an antibody which binds CD40. Given the well known use and practice of recombinant technology to produce homogeneous proteins at the time the invention was made, engineered CD40-specific antibodies as well as engineered cytokines encompassed by the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. The patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113.

Further, given the teachings of Maraskovsky et al. of vaccinating for tumor antigens, including the use of CD40:CD40 ligand pathway and IL-2 (see above) and the teachings of McHugh et al. for teaching the provision of co-stimulatory signals in conjunction with tumor cell vaccination, the ordinary artisan would have been motivated at the time the invention was made to combine the co-stimulatory signal of anti-CD40 antibodies, taught by Dullforce et al., Caux and Heath, in conjunction with the tumor cells themselves to vaccinate against tumor cells and/or antigens of interest. It would have been immediately apparent to one of ordinary skill in the art that tumor cells would have been attentuated so that tumor cells would not be able to divide and proliferate in a host. If not, the tumor cells could proliferate to the point of being detrimental to the subject fo the vaccination.

Jacquier-Sarlin et al. teach the use of complement fragments including C3b to enhance immune responses to antigens of interest (see entire document). By increasing antigen processing and presentation, C3b could be engineered into new vaccines (see Discussion, particularly the last paragraph on page 169).

Given the teachings of Jacquier-Sarlin et al. that C3b which would include the alpha chain of C3b, increases antigen processing and presentation which would be useful for engineering vaccines, one of ordinary skill in the art would have been motivated to incorporate C3b into vaccine preparations to a host of pathogenic organisms and antigens, including tumor antigens in order to increase immunogenicity and, in turn, increase immune responses to antigens of interest.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Jacquier-Sarlin to incorporate C3b into the methods of vaccination via alternative modes of compositions comprising immunogenic cells, anti-CD40 antibodies and IL-2, as taught above to obtain vaccination by a highly immunogenic composition to pathogenic organisms of interest, including tumor cells. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose, which is increasing immunogenicity in methods of vaccination in the instant case. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive, given the newly added reference Hoo which addresses applicant's arguments concerning the recitation of "admixture with a ligand for CD40 which comprises a heterologous cell membrane binding moiety".

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
June 24, 2005